City of Hope

Karen S. Aboody, M.D.
Associate Professor
Departments of Neurosciences and Neurosurgery

Beckman Research Institute
1500 East Duarte Road
Duarte, California 91010
tel: 626-471-7177
fax: 626-301-8857
email: kaboody@coh.org

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Robert Klein, J.D., Chair
Independent Citizens' Oversight Committee
Alan Trounson, Ph.D.
President and Chief Scientific Officer
California Institute for Regenerative Medicine

Re: Extraordinary Petition
DR1-01421: Stem Cell-Mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials

Dear Mr. Klein, Dr. Trounson, and Distinguished Members of the ICOC,

Thank you for the opportunity to submit a CIRM Disease Team grant proposal for funding consideration. With due respect for the peer review process of the Grants Working Group, I would like to bring to your attention the certain key points of our proposal that may not have been fully appreciated by the review panel.

I appreciate the helpful discussions with CIRM scientific staff and your attention in providing me the opportunity to submit an Extraordinary Petition in support of our Disease Team Proposal *DR1-01421: Stem Cell-Mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials.* Attached is a 3 page petition highlighting key points and considerations for your review.

The potential impact of our proposal, for the treatment of recurrent gliomas and other malignant brain tumors is substantial, as these patients do not fare well on currently available surgical, chemo-, and radio- therapies. Our pioneering work with neural stem cell-mediated cancer therapy offers tremendous promise for treating these invasive brain tumors, as they have the unique ability to selectively target therapeutics to invasive tumor foci throughout the brain. Our proposed therapy has the potential to greatly advance this field by overcoming the obstacles responsible for conventional treatment failures, and leading to improved clinical outcome.

We sincerely appreciate the commitment of CIRM and its governing board in supporting and accelerating the best, most advanced science for translation to clinical applications, and appreciate your consideration of our petition for funding.

Respectfully,

Karen S. Aboody, MD

Extraordinary Petition DR1-01421: Stem Cell-Mediated Therapy for High-grade Glioma: Toward Phase I-II Clinical Trials

Background: Patients with high-grade gliomas, that strike people at any age, have survival times measured in months. Novel therapies are both critically needed and justified for testing in this patient population, because the benefit to risk ratio is extremely high. The potential impact of our proposal for treatment of recurrent gliomas and other malignant brain tumors is substantial, as these patients ultimately fail currently available surgical, chemo-, and radio-therapies. Our approach is to harness the intrinsic tumor-targeting ability of neural stem cells (NSCs) to deliver cytotoxic agents directly and selectively to glioma sites and destroy them. Successful implementation of this proposed therapy would lead to vastly improved survival outcome and quality of life for these patients.

Leadership: As the Principal Investigator (PI) I have pioneered development of the field of NSC-mediated cancer treatment for the past 14 years, and was first author of the seminal publication demonstrating the phenomenon of neural stem cell homing to invasive brain tumors, and proof-of-concept for therapeutic efficacy in glioma models (Aboody et al., Proc Natl Acad Sci, 2000). I have since developed this therapy, demonstrating selective NSC targeting of tumor sites using 2 therapeutic enzyme/prodrug strategies in pre-clinical models of glioma (Lin et al, NeuroImage, 2007; Kendall et al, Stem Cells, 2008; Zhao et al, Mol Can Res, 2008); melanoma brain metastasis (Aboody et al, Neuro-Onc, 2006), medulloblastoma (Kim et al, Clin Canc Res, 2006); and further demonstrated intravenous delivery of NSCs to target solid tumors both inside and outside the brain (Brown et al. Hum Gene Ther, 2003), including metastatic neuroblastoma (Aboody et al, PLoS ONE, 2007; Danks et al, Canc Res 2008). In all models, we and other groups demonstrate selective homeing of NSCs to invasive tumor sites and their therapeutic potential using a variety of anti-cancer agents. (reviewed in Aboody et al, Gene Ther, 2008) and therapeutic potential. I am co-inventor on 2 issued patents for the use of NSCs to target therapeutic agents to brain tumors and metastatic solid tumors (US Patent nos. 7,186,409 and 7,393,526). Gaining expertise at Harvard in neurogenetics, neuro-oncology and stem cell biology, in Industry R & D as a senior scientist, and in my current position directing a translational stem cell laboratory at City of Hope, I believe I am uniquely qualified to move this specific research approach from the laboratory to the clinic.

Disease Team: During the past several years, I have formed an effective, multidisciplinary team encompassing preclinical research and development, regulatory affairs, cGMP manufacture and testing, clinical oncology and neurosurgery in order to translate this approach from the bench to the bedside. As detailed below (**1a-g**), in the last 4 years, my team has successfully completed the necessary testing and regulatory approvals, to be the first in the world to submit an IND to the FDA for the first-in-human study of NSC-mediated therapy for recurrent brain tumor patients. Specifically, our IND is now in review with the FDA, for use of our cytosine deaminase (CD)-expressing NSCs in combination with the oral pro-drug 5-Flurocytosine (5-FC) to produce 5-Fluoruracil (5-FU) at tumor sites to treat recurrent glioma patients. Our CIRM proposal significantly advances this therapeutic paradigm, while following similar preclinical development, cGMP manufacture, and regulatory timelines.

Therapeutic Approach: We have submitted an IND for use with the pro-drug 5-FC. Our CIRM proposal applies our established, banked and NIH-approved NSC line to advance the scope of therapeutics beyond 5-FU, which although efficacious, is unlikely to be curative in recurrent glioma patients. We propose to modify our NSCs to secrete an enzyme, carboxylesterase (CE), that will activate CPT-11 to SN-38 at the tumor sites, delivering an extremely potent chemotherapeutic. Our group and others now know that SN-38 is 1000x more effective than 5-

FU in killing malignant cancer cells with the potential to fully eradicate them. Further, CPT-11 (Irinotecan) is a first line chemotherapeutic for colon cancer and metastatic neuroblastoma, and is currently in Phase II clinical trials for glioma patients. In our proposal, we cited our studies demonstrating substantial therapeutic efficacy of this novel enzyme approach in pre-clinical metastatic solid tumor models of neuroblastoma: our approach cured 90% of mice at 1 year, compared to 0% for untreated mice and 30% for mice receiving CPT-11 alone. This is one of the most successful stem cell-based approaches to cancer therapy thus far reported in a preclinical tumor model. In our proposal, we present and cite data demonstrating the promise of this same strategy for malignant gliomas.

I would like to summarize the following key points of our proposal:

1. The RFA states that "The mission of these teams will be to conduct the necessary research and regulatory activities to prepare and file a complete, well supported Investigational New Drug Application (IND) with the Food and Drug Administration (FDA) (and, if desired, other regulatory agencies), to enable Phase I clinical testing", in 4 years.

We were surprised by the reviewers' comment that we were "unlikely to succeed in IND submission within 4 years". As stated in the proposal, in the past 4 years (2006-2009) my established team has already successfully:

(a) submitted a pre-IND and conducted ongoing conferences with the FDA (2006-2009)
(b) established a stable, fully release-tested cGMP master cell bank of human neural stem cells for patient use under the direction of my co-PI, Dr. Couture. This same NSC bank can be further modified for future IND submissions.
(c) been the first to receive unanimous consent from the NIH Recombinant DNA Advisory Committee (RAC) for a genetically engineered human neural stem cell line for use in recurrent glioma patients
(d) completed the necessary safety, tumorigenicity, immunogenicity, toxicology, therapeutic efficacy and other IND-enabling studies designed to model conditions of the clinical trial
(e) completed the clinical protocol and consent forms, written by my co-PI, Dr. Portnow (clinical PI on our current IND and proposed clinical PI on our CIRM proposal)
(f) obtained the Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC) approvals required for IND submission
(g) filed an IND for a first-in-human NSC-mediated CD/5FC treatment phase I trial for recurrent glioma patients. Our IND is currently in review with the FDA.

Taken together, my team has clearly demonstrated that we have the experience, expertise, infrastructure, technology and track record to move a more effective NSC-mediated treatment approach to IND submission within 4 years.

2. The RFA indicates that projects are supposed to be in pre-clinical development/IND-enabling stage with a development candidate already identified and proof-of-concept demonstrated.

(a) Our proposal starts with our NIH approved NSC line (F3.CD NSCs) which has been established for clinical use as a fully release-tested Master Cell Bank at the COH cGMP facility. We have already demonstrated chromosomal stability, high tumor-targeting activity, safety and efficacy with these cells. This is an expandable, clonal NSC line, meaning that every cell is identical, with the advantage that we can expand the population of cells by many millions – to generate as many vials as necessary for future therapeutic modification and clinical trials without needing new sources of cells.

(b) We have already demonstrated therapeutic efficacy of our NSC line using two enzyme/prodrug strategies (CD + 5-FC → 5-FU and CE + CPT-11 → SN-38) strategies in animal models of glioma, medulloblastoma, solid tumor brain metastasis and metastatic neuroblastoma. Preliminary data with our NSCs support the testing and comparison of two forms of CE, for which both vectors are in hand and ready for further development, manufacture and use in IND-enabling studies.

Therefore, our development candidate is clearly identified as specified in the RFA. Our therapeutic vectors are also developed and tested. We have already demonstrated NSC.CE + CPT-11 → SN-38 proof-of-concept for tumor targeting and therapeutic efficacy, and have proposed the safety, toxicology and therapeutic efficacy, preclinical glioma IND-enabling studies to optimize safety and therapeutic regimens.

3. Criticism of our review focused on our choice of therapeutics. In fact, we have been extremely strategic in our design of therapeutics. Because studies by our group and others indicate that 5-FU alone is unlikely to be curative, we now propose a much more promising enzyme/prodrug strategy, CE + CPT-11 → SN-38, that is strongly supported by the literature. Our team has therefore further modified our NSC line to secrete CE. As stated in our proposal, the exceptionally high toxicity of SN-38 treatment (approximately 1000-fold higher than 5-FU) has been demonstrated for numerous malignant tumors, with literature supporting the current use of CPT-11 in Phase II clinical glioma trials. In our proposal, we outlined a comparison of two forms of the CE enzyme (rabbit or modified humanized CE), which have demonstrated up to 70-fold higher specific activity in converting CPT-11 to SN-38 than native human CE's. In this respect, reviewers expressed concern over our preliminary microdialysis data – which demonstrated 1-2% conversion of CPT-11 to SN-38 by NSC-delivered CE in the brain. However, there is normally no CPT-11 activating CE in the brain (native CEs are located mainly in the liver and gut). The significance of this data is that we are secreting a highly active form of CE to produce SN-38 localized specifically to the brain tumor sites. Preliminary and cited data clearly demonstrate the high sensitivity of glioma to SN-38, and feasibility and proof-of-concept of our therapeutic strategy has been demonstrated *in vitro* and *in vivo.* It is the purpose of this proposal to quantify CE activity for selection of the best (most active) form of CE for clinical development. We will compare NSC doses and CPT-11 regimens to optimize the concentration of SN-38 produced in the brain for maximum efficacy and safety. Our proposed studies employ both established and patient-derived glioma lines. Clear, quantitative milestones and go/no go decisions for efficacy and safety are provided.

4. Reviewers described our scientific rationale as sound and our strategy as elegant. They praised the maturity of our regulatory strategy, having proposed timely meetings with the FDA to review and discuss IND-enabling studies. Our candidate selection criteria were clearly stated.

5. Potential future impact of NSC-mediated cancer treatment. The advantage of our developmental pipeline, having already established an expandable NSC line, is that these same cells can be further modified with different therapeutic genes. Success of this treatment approach for glioma will pave the way for NSC-meditated treatment for other invasive and metastatic solid tumors in the brain, as well as metastatic tumors throughout the body.

In summary, we have the team, the expertise, the track record, the cells and materials, and the environment necessary to carry our new project to IND submission within 4 years. We sincerely appreciate the commitment of CIRM and the Members of the ICOC to supporting the best, most advanced science for translation to clinical applications, and appreciate your consideration of our petition for funding.